

## Spontaneous dissemination of DKA prevention campaign successfully launched in Nineties in Parma's province

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**Summary.** *Aim:* to investigate how much effectiveness of the historical campaign of DKA prevention at T1D diagnosis has survived in Parma's province where this was launched in Nineties, and how much it has spontaneously spread in the neighboring provinces. *Method:* children aged 6-14 years with newly diagnosed T1D coming from province of Parma (Group 1) and from two other nearby provinces (Group 2) were investigated. Clinical and laboratory data were retrospectively collected from medical files of each patient and included age, gender, capillary pH, serum bicarbonate, 3-beta-hydroxybutyrate (3HB), glycated hemoglobin (HbA1c) at the time of admittance from 1st January 2012 and 31 December 2016. *Results:* no DKA condition was globally found in 25/36 patients (69.4%): 16/17 and 9/19 patients belonged to Group 1 and 2 respectively ( $p=0.002$ ). Mild or moderate DKA was reported in 5.9% patients of Group 1 and in 47.31% ( $p=0.005$ ) patients from Group 2. Severe DKA was observed in only 1 child from Group 2. Normal 3-beta-hydroxybutyrate (3HB) serum levels was reported in the 25 patients without DKA at diabetes diagnosis. Duration of hyperglycemia-related symptoms before overt T1D diagnosis was shorter ( $4.6\pm 2.5$  days) in patients with 3HB levels  $<1$  mmol/dl than in those with 3HB levels exceeding 1 mmol/dl ( $9.6\pm 4.2$  days,  $p<0.0001$ ). HbA1c values were on average lower in patients without DKA ( $9.9\pm 1.2\%$ ) than in patients with DKA at diabetes diagnosis ( $13.60\pm 1.3\%$ ;  $p<0,001$ ). *Conclusion:* 1) the campaign for DKA prevention, launched in Nineties and renewed at beginning of Twenties in Parma's province, continues to be effective in the same province after several years; 2) in the two control provinces despite no information campaign being officially promoted in loco, an unexpected decrease in severe DKA incidence as well a shorter latency before overt T1D diagnosis were observed in the same period. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** type 1 diabetes, diabetes ketoacidosis, DKA prevention, Parma campaign, enuresis, childhood

### Introduction

Diabetic ketoacidosis (DKA) is a frequent complication in newly diagnosed diabetic children, generally reported in 12 to 80% of patients (1). When it is unrecognized DKA can be burdened by severe consequences such as impairment of consciousness and even death (2). DKA frequency in Italy has been evaluated

on 40.3% with 29.1% and 11.2% for mild/moderate and severe DKA, respectively (3).

DKA is usually related to misdiagnosed hyperglycemia-associated symptoms (1). Only a small percentage of parents reports to have promptly linked to the diabetes frequent urination, excessive thirst and weight loss observed in their child before overt disease clinical diagnosis (4). It has been described that about 40%

of children presenting DKA were seen by a primary healthcare practitioner at least once closely to the Type diabetes (T1D) diagnosis without a clinical suspect being formulated (1). In this way, potential chances of preventing DKA are irreparably lost.

How to shorten this delay in diagnosis is still a topic of open discussion. In 1991-1997 our group demonstrated that, thanks a capillary school and physician awareness campaign in Parma, Italy, centered on the earliest symptom of T1D reported by 89% of parents (wetting the bed in a child usually “dry”), it was possible to decrease greatly the DKA rate in newly diagnosed diabetic children (5). Eight years later the historical campaign, the same Authors showed in a retrospective investigation (1999-2006) that prevention campaign was still effective, and that unexpected enuresis episodes observed in a “dry” child confirmed to be a reliable warning symptoms to promptly diagnose T1D at onset, and to maintain DKA rate low (6).

Similar campaigns based on Parma study were launched in Australia and in France with great impact on DKA prevention (7, 8), while the poster campaign promoted in Wales in 2008 carried out with the same purpose did not give expected results because of a reported lack of personal engagement (9).

In the present paper we investigated how much effectiveness of the historical campaign has survived at ten years from the last check at 2006 (6). For this purpose we analyzed the five years most distant from a time perspective (2012 - 2016).

## Patients and methods

Investigation was limited to the children aged 6-14 years with newly diagnosed T1D coming from province of Parma and from two other nearby provinces located in the same Emilia Romagna Region, admitted to the Department of Pediatrics of Children Hospital “Pietro Barilla” at the University Hospital of Parma, Italy, from 1<sup>st</sup> January 2012 and 31 December 2016. The above provinces were the same areas of Northern Italy where historical Parma campaign for DKA prevention was launched in the Nineties according the procedures published elsewhere (5, 6).

In Parma province only a capillary awareness campaign addressed to parents and physicians was re-launched between 2007 and 2010 displaying traditional posters and leaflets in pharmacies and pediatricians offices, and through local radio announcements, after five episodes of severe DKA were observed in 2004 and 2006 period (6). This intervention was also supported by a toll free phone number directly connected with diabetes team of our department. In the other two provinces no structured campaign was promoted directly by our group. However given the results obtained in the province of Parma in the previous campaigns we can speculated that some anecdotic preventive initiatives were spontaneously launched by local pediatricians.

In addition to these targeted interventions, since 2006 one of the authors of this paper (M.V) has described to the students of the last year of Medicine and Pediatrics schools at the University of Parma, the Parma’s campaign strategy by 2-hour lessons each year. These lessons were attended by a total of 1,310 newly graduates in Medicine and in Pediatrics between 2012 and 2016.

To allow Parma campaign messages to reach as many people as possible, a section dedicated to T1D precious diagnosis was included in the App menu called “Kids and Teens Diabetes” for mobile devices. This quick guide, free available in fifteen languages, was created in 2014 by one of the author (M.V) to help children, adolescents, parents, teachers, pediatricians and nurses in managing T1D at school, at work, during exercising or traveling or driving or partying.

DKA at diabetes diagnosis was classified regarding to severity of the acidosis as *mild* with venous pH<7.3 or bicarbonate <15 mmol/L; *moderate* with pH<7.2, bicarbonate <10 mmol/L; and *severe* with pH<7.1, bicarbonate <5 mmol/L. No DKA status was defined as a metabolic condition characterized by venous pH>7.3 or bicarbonate >15 mmol/L and blood glucose >200 mg/dl, without ketonemia and ketonuria.

Data for this study were collected from medical files of each patient and included age, gender, capillary pH, serum bicarbonate, 3-beta-hydroxybutyrate (3HB), glycated hemoglobin (HbA1c). 3HB serum levels were tested on a fingerstick blood specimen by a simple-to-use hand-held device (Medisens

Optium Xceed, Abbott Laboratories, Bedford, MA, USA). 3HB serum levels  $<0.5$  mmol/dl were defined as *normal*; levels exceeding 1 mmol/dl were retained as *hyperketonemia or ketosis*; and levels in excess of 3.0 mmol/dl were classified as *ketoacidosis* (10). HbA1c levels were measured by the Bayer DCA 2000 method (upper limit of normal value: 6.0%).

Parents of patients admitted to our department are used to sign an informed consent document for the use of clinical data regarding their children for scientific purposes only. No conflict of interest exists in relation to the subject matter of present paper.

### Statistical analysis

Data were summarized as numbers (n) and frequencies (%) if they were categorical and as mean and standard deviation (SD) if quantitative. If the data were normally distributed a two-tailed unpaired T-test or otherwise a non-parametric Mann-Whitney U-Test was applied to compare results between groups. Chi-square test ( $\chi^2$ ) or Fisher exact test was used to compare frequencies between groups. A p value  $<0.05$  was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 21.0.

### Results

From 1<sup>st</sup> January 2012 to 31<sup>st</sup> December 2016, 135 children aged 1 to 18 years with new-onset T1D were admitted to the Department of Pediatrics, Children University Hospital of Parma, Italy. Thirty-six of these patients (26.6%) were 6-14 years old (22 boys and 14 girls; mean age  $10.2 \pm 3.3$  SD): 17 (11 boys and 6 girls;  $11.6 \pm 3.4$  years old) came from the province of Parma (Group 1) and 19 (11 boys and 8 girls;  $10.4 \pm 2.2$  years old) came from other two nearby control provinces (Group 2).

No DKA condition was globally found in 25/36 patients (69.4%): 16/17 (94.1%) and 9/19 (47.31%);  $\chi^2$ : 9.24,  $p=0.002$ ) patients belonged to Group 1 and 2 respectively. Mild or moderate DKA was reported in 1/17 (5.9%) patients of Group 1 and in 9/19 (31.0%;

$\chi^2$ : 7.70,  $p=0.005$ ) patients from Group 2. Severe DKA was observed in only 1 child from Group 2. Impaired level of consciousness was not found in any patients. The new T1D diagnosis were homogeneously distributed within the period 2012-2016 in both patient Groups.

Normal 3HB serum levels ( $<0.5$ -1 mmol/dl) were reported in the 25 patients without DKA at diabetes diagnosis. A ketonemia between 2 and 3 mmol/dl was observed in 8 children affected by a mild (n. 2) or moderate (n. 6) DKA. 3HB levels exceeding 3 mmol/dl were found in 3 patients with severe DKA.

Duration of hyperglycemia-related symptoms before overt T1D diagnosis was shorter ( $4.6 \pm 2.5$  days) in patients with 3HB levels  $<1$  mmol/dl than in those with 3HB levels exceeding 1 mmol/dl ( $9.6 \pm 4.2$  days;  $t=4.46$ ,  $p<0.0001$ ).

HbA1c values were on average lower in patients without DKA ( $9.9 \pm 1.2\%$ ) than in patients with DKA at diabetes diagnosis ( $13.60 \pm 1.3\%$ ;  $t=8.31$ ,  $p<0,001$ ).

### Discussion

Two interesting data come out from today's study: 1) the campaign for DKA prevention, launched in Nineties and renewed at beginning of Twenties in Parma's province, continues to be effective in the same province after several years; 2) in the two control provinces despite no information campaign being officially promoted *in loco* during study observation, an unexpected decrease in severe DKA incidence as well as a shorter latency before overt T1D diagnosis were observed in the same period.

The percentage of newly diagnosed diabetic children without DKA in Parma's province between 2012 and 2016 (94.1%) has further increased compared to that reported in 1999-2006 (84.3%) (6). The goal is even more impressive when one considers that no cases of severe DKA were recorded, and that the incidence of cases with mild or moderate DKA in the same period showed a tendency to approach zero. These results are not casual and may be attributed to the high level of attention on early symptoms of T1D at onset produced by a targeted and uninterrupted awareness campaign with pediatricians, parents, and primary health-

care practitioners in Parma's province. This speculation is supported by the finding that in newly diagnosed children with T1D coming from the two control provinces where prevention program was not carried out, the frequency of mild to severe DKA continues to be high and close to that observed at the historical follow-up studies on Parma's campaign in 2006.

Despite this discrepancy, an improvement in cases without DKA and a decrease in DKA severe status at T1D diagnosis were observed also in children from the control provinces. These unexpected data may be related with the shorter period of metabolic derangement preceding the appearance of overt diabetes observed also in these control provinces. Newly diabetic children coming from this area showed a shorter latency period than that reported in 1999 ( $9.6 \pm 4.2$  vs  $28.0 \pm 10.0$ ).

These results may be attributed to a spontaneous sensitization towards Parma's campaign program in these areas thanks to spontaneous anecdotic initiatives promoted by pediatricians or parents' association of children with T1D. At least two other explanations may be hypothesized to interpret this "osmotic" involvement. The first one concerns Parma's campaign messages which have been communicated each year to the newly graduates in Medicine and in Pediatrics since 2012 at the University of Parma. Some of these physicians and pediatricians were from the two control provinces and they have been facilitated in implementing in their origin areas the teaching learned at the university. The second hypothesis refers to the App named "Kids and teens diabetes" published by one of the Authors (M.V.) of this paper to help teenagers, parents and physicians in trouble with T1D management. In the menu of this App there is a chapter dedicated to Parma's campaign messages. Being this application free access one can assume that it has been consulted by a large number of people interested in T1D as parents and pediatricians.

Decreased incidence in DKA reported in all provinces involved in Parma's campaign follow up may be attributed to the shorter period of relative insulin deficiency status preceding overt diabetes diagnosis. This speculation is supported by the observation of normal or slightly increased in 3HB levels in our newly diagnosed children without DKA. It is known that even 50-100  $\mu\text{U/ml}$  of circulating insulin are sufficient to

stop lipolysis (11). The appearance of unusual and repeated enuresis episodes in a child usually "dry" in recognizing the latency period has a crucial role, and this symptom confirms to be once again the most important warning symptom for the early diagnosis of T1D and for DKA prevention.

Some authors have interpreted the results up to date obtained with Parma's campaign as limited by the small number of children enrolled in the studies (12). Our group works in an area of Northern Italy where the annual incidence of new cases of T1D is 10.3:100.000 children aged 6-14 years. The newly diagnosed diabetic children from Parma area is thus proportional to the young population living in this province. Regardless of the number of patients studied it is unquestionable that Parma campaign has produced remarkable results in terms of DKA prevention at T1D onset.

Working in a small province like Parma is a further point of strength for our study. This allowed us to promote a widespread campaign and monitor the effective cooperation especially by school teachers, pediatricians and general practitioners. We have observed, for example, that school teachers collaboration was reduced over time under the pressure of family associations that required equal attention for other diseases such as epilepsy, autism, and obesity. We have consequently restricted our intervention into the school to the World Diabetes Day by providing teachers with traditional posters and leaflets of Parma's campaign with the request to discuss about with students and families.

A further facility concerned the continuous dialog between pediatricians and our team facilitated by the availability of a toll free phone number implemented in our department by parents association of children with T1D. This communication system helped us to maintain alive physicians attention at the early signs of a latent hyperglycemia because we are convinced that DKA prevention requires increased awareness of T1D symptoms not only by parents but also by primary healthcare practitioners. It is impressive that a lot of children presenting DKA are in vain seen by a doctor at least once before diagnosis (1).

In conclusion, the results of the present study confirm retrospectively those previously published by our group (4,5) and demonstrate that by means of an

aggressive and periodically renewed campaign of information on the early symptoms of T1D at onset it is possible to obtain a progressive and long lasting decrease in DKA complication in newly diagnosed diabetic children.

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